

Response to Chemotherapy and Predictors of Survival in Adult Rhabdomyosarcoma

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Objective

To assess outcome and identify predictors of survival of adults with rhabdomyosarcoma.

Summary Background Data

The literature on adult rhabdomyosarcoma is limited. Few studies have identified predictors of long-term survival in this patient population.

Methods

Thirty-nine adults with rhabdomyosarcoma were treated between 1973 and 1996 and prospectively followed. Outcomes were assessed with respect to patient and tumor characteristics, local treatment, and response to chemotherapy.

Results

Twenty-six patients had localized/locoregional disease and 13 patients had metastatic disease at presentation. Twenty-one patients underwent attempted curative resection, 27 received radiotherapy, and 37 received chemotherapy. Median follow-up for surviving patients was 152 months. The overall 5-

and 10-year survival rates were 31% and 27%, respectively. Five-year survival rates for patients with tumors less than 5 cm, 5 to 10 cm, and more than 10 cm were 60%, 14%, and 0%, respectively. Patients with localized/locoregional disease at presentation had a 44% 5-year survival rate; there were no 5-year survivors among patients with metastatic disease. Patients who had a complete response to chemotherapy had a 5-year survival rate of 57%, compared with a rate of only 7% for poor responders. Metastatic disease at presentation and poor response to chemotherapy were independent predictors of death on multivariate analysis.

Conclusions

Age, location, nodal status, and histologic subtype do not appear to be associated with survival in adults with rhabdomyosarcoma treated with multimodal therapy. Metastatic disease at presentation and poor response to chemotherapy are strongly associated with poor prognosis. Future systemic therapies should be targeted to patients with localized/locoregional disease and partial responders to conventional chemotherapy.

Rhabdomyosarcomas are the most common soft tissue sarcomas of childhood, representing 4% to 8% of all malignant disease in children younger than 15 years old.¹ They can occur within mesenchymal tissue at any site, although they have a predilection for the head and neck and genitourinary tract. The embryonal subtype is the most common,

representing up to 60% to 80% of tumors at the above sites. The botryoides subset of embryonal lesions develops in the walls of viscera, such as the nasopharynx, bladder, or vagina, and carries a better prognosis.² Alveolar tumors are more common among adolescents, often arise in the extremities, and carry a worse prognosis.^{3,4} Pleomorphic tumors are characterized by "MFH-like" morphology with bizarre-appearing cells, are rare in children, and arise mainly in deep soft tissues.

Rhabdomyosarcomas behave aggressively and often show evidence of early disseminated disease.¹ Recent improvements in pediatric survival rates have been largely attributed to the widespread use of combined chemotherapy

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regimens, particularly in patients with orbital and genitourinary tract primaries. Recent series have reported improvements in the 5-year survival rate from 5% to 15% with local therapy alone to 47% to 62% with multimodal therapy.⁵⁻¹⁰

Rhabdomyosarcomas are rare in adults, and the literature regarding their management is limited. Truncal and extremity tumors are more common in adults, and the relative proportion of pleomorphic tumors increases with age. Despite the recent use of multimodal therapy, the prognosis in older patients appears to be worse than in children.¹¹⁻¹³ In this series, we reviewed our experience with a large number of adult patients with rhabdomyosarcoma treated with multimodal therapy. The aim of this study was to assess the response to systemic chemotherapy and to identify clinicopathologic and treatment-related predictors of long-term survival in this population.

PATIENTS AND METHODS

Patients and Clinicopathologic Variables

From 1973 to 1996, 39 adults (16 years or older) with rhabdomyosarcoma were evaluated at the Brigham and Women's Hospital and the Dana Farber Cancer Institute. Thirty-eight patients presented at the time of initial diagnosis and one patient presented with a local recurrence after resection at another institution. Patient, tumor, treatment, and survival data were prospectively acquired and entered into our sarcoma database.

Patient demographics included age at diagnosis and gender. Location of tumor was divided into head and neck, trunk, genitourinary tract, and extremity. The trunk group included tumors of the thorax, abdominal and pelvic retroperitoneum, and perineum. The extremity group consisted of tumors involving either the girdle musculature or the extremities. Tumor size (<5 cm, 5-10 cm, >10 cm) was based on the largest dimension of the primary tumor as reported in pretreatment computed tomography (CT) and/or magnetic resonance (MR) scans. Nodal involvement was based on bulky adenopathy on physical examination, imaging studies, and/or lymph node sampling at the time of surgery. Distant metastases were identified by imaging studies and/or the presence of tumor cells on bone marrow aspirates. Disease stage was assigned using the 1992 AJCC staging system. Histologic subtype was divided into embryonal, alveolar, pleomorphic, and not otherwise specified (NOS). All 39 cases were rereviewed and histologically confirmed by two of the authors (B.P.R., C.D.M.F.) with respect to histologic type and subtype.

Local treatment consisted of surgery, radiation therapy, or both. Enucleations and subtotal excisions were classified as noncurative resections, whereas wide excisions, compartmental resections, and amputations were classified as attempted curative resections. Specimen margins were analyzed for evidence of microscopic disease. Attempted curative resections with microscopically negative margins

were considered complete. Attempted curative resections with microscopically positive margins or evidence of nodal involvement were considered compromised. Partial resections or attempted curative resections with grossly positive margins were considered incomplete. Radiation therapy consisted of external beam radiotherapy, with or without additional brachytherapy. Radiotherapy was administered in the preoperative setting, the postoperative setting, or both.

All patients were offered systemic chemotherapy, and two patients refused: a 46-year-old man who underwent complete resection of a 3-cm, pleomorphic rhabdomyosarcoma of the thigh, and an 82-year-old man who underwent complete resection of a 7-cm, pleomorphic rhabdomyosarcoma of the triceps muscle. Both patients received postoperative radiotherapy. Chemotherapy was administered in the preoperative setting, the postoperative setting, or both. Systemic chemotherapy consisted of one of several doxorubicin-based or ifosfamide-containing regimens. Response to chemotherapy (complete vs. partial vs. none vs. progression of disease) was based on the observed change in the size of the primary tumor on pre- and posttherapy CT/MR scans, and/or the presence of residual disease at the time of resection. For patients who underwent resection of their primary tumor before the initiation of chemotherapy, response to chemotherapy was based on change in size of preexisting metastases during therapy. Response could not be assessed in four patients for the following reasons: complete resection of localized disease before initiation of therapy (two patients), refusal to complete chemotherapy (one patient), and chemotherapy-related death (one patient).

Patients were followed in our Soft Tissue Sarcoma Program at 3- to 4-month intervals during the first 2 to 3 years and at 4- to 6-month intervals thereafter. Information obtained during follow-up included status (alive without disease, alive with recurrent disease, dead without evidence of recurrent disease, dead as a result of sarcoma treatment or with sarcoma), recurrence (type, location, timing), salvage therapy, and results of salvage therapy.

Statistical Analysis

Age was treated as both a continuous and dichotomous variable, using median age as the breakpoint for the statistical analysis. For the analysis, patients with stage 3a and 3b disease were combined into a single (stage 3a-b) group, as were patients with pleomorphic and NOS tumors. Patients who received preoperative therapy (e.g., radiotherapy, chemotherapy) and patients who received combined pre- and postoperative therapy were analyzed as a single group in the statistical analysis. Patients who received both doxorubicin and ifosfamide were placed in the ifosfamide regimen group in the analysis. Patients who showed a partial response, no response, or progression of disease while receiving chemotherapy were combined and treated as poor responders. The univariate relationships between the continuous variables and the dichotomous/categorical variables were analyzed

using the Kruskal-Wallis test. The univariate relationships among the dichotomous/categorical variables were analyzed using the Fisher exact test. The univariate relationships between response to chemotherapy and the various clinicopathologic variables were analyzed using the Fisher exact test.

Patient outcome (overall survival) was assessed with respect to the following clinicopathologic and treatment-related variables: age, gender, location of primary, tumor size, nodal involvement, stage at presentation, histologic subtype, and response to chemotherapy. All deaths were due to either progression of disease (26 patients) or treatment toxicity (1 patient). Survival was measured from the time of diagnosis to the time of death or last follow-up.

Survival curves were constructed by the Kaplan-Meier product limit method.¹⁴ The log-rank test of survival analysis was used to identify univariate predictors of overall survival.¹⁵ Univariate predictors of survival were entered into a Cox proportional hazards model using stepwise selection to identify independent predictors of death.¹⁶

The impact of local treatment (surgery and/or radiotherapy) and the timing and type of chemotherapy regimen on long-term survival was analyzed separately. The effect of secondary or salvage treatments was not included in the analysis.

RESULTS

Patient and Tumor Characteristics

The clinicopathologic and local treatment characteristics of the 39 patients included in this study are shown in Table 1. The median age was 26 years (range 16–82), and 75% of the patients were older than 20 years. Most of the patients were male ($n = 24$, 62%). Thirteen patients had head and neck tumors in the following sites: orbital (six patients), paranasal sinuses (three patients), and scalp, face, oral cavity, and oropharynx (one patient each). The trunk group included seven patients with tumors involving the thorax (two patients), abdominal or pelvic retroperitoneum (two patients), and perineum (three patients). The genitourinary tract group consisted of seven patients with prostatic (three patients), paratesticular (two patients), uterine (one patient), and bladder (one patient) tumors. The extremity group consisted of 2 patients with tumors of the girdle musculature and 10 patients with limb tumors.

The median tumor size was 6.0 cm (range 1–35); truncal and genitourinary tract tumors were statistically larger. The median sizes of genitourinary tract, truncal, extremity, and head and neck tumors were 11, 6.5, 5.3, and 4 cm, respectively ($P = .007$).

Eighteen patients (46%) had clinical or pathologic evidence of nodal involvement at presentation. Most patients had localized or locoregional disease: stage 3a (5 patients), stage 3b (10 patients), and stage 4a (11 patients). Thirteen patients with stage 4b disease with metastases to the fol-

Table 1. PATIENT DEMOGRAPHICS, TUMOR CHARACTERISTICS, AND LOCAL TREATMENT (N = 39)

	Disease at Diagnosis		
	Localized/ Locoregional	Metastatic	All Patients
No. of patients	26	13	39
Age, median (yr)	27	24	26
Sex			
Male	16	8	24 (62%)
Female	10	5	15 (38%)
Location			
Head and neck	10	3	13 (33%)
Trunk	5	2	7 (18%)
Genitourinary tract	3	4	7 (18%)
Extremity	8	4	12 (31%)
Size (cm)			
<5	13	2	15 (38%)
5–10	11	5	16 (41%)
>10	2	6	8 (21%)
Nodal involvement			
Negative	15	6	21 (54%)
Positive	11	7	18 (46%)
Histology			
Embryonal	4	3	7 (18%)
Alveolar	14	8	22 (56%)
Pleomorphic	5	0	5 (13%)
NOS	3	2	5 (13%)
Surgery			
Biopsy only	5	6	11 (28%)
Subtotal excision	6	1	7 (18%)
Complete excision	15	6	21 (54%)
Radiotherapy ($n = 27$)			
Preoperative	5	3	8 (33%)
Postoperative	16	0	16 (67%)

NOS, not otherwise specified.

lowing sites were treated: lung (five patients), bone (five patients), peritoneal cavity (two patients), and pleura, liver, retroperitoneum, distant nodes, and skin (one patient each). In this series, no patients with stage 4b disease were treated before 1985.

Increasing tumor size was associated with distant metastases at presentation. Thirteen percent of patient with tumors smaller than 5 cm had evidence of metastases, compared with 31% and 75% of patients with tumors measuring 5 to 10 and more than 10 cm, respectively ($P = .01$). Most patients ($n = 22$) had alveolar rhabdomyosarcomas; 7 and 10 patients had embryonal and pleomorphic/NOS tumors, respectively.

Local Treatment and Systemic Therapy

Details of local treatment are given in Table 1. Twenty-eight patients underwent surgical excision of their primary tumor. Seven patients underwent noncurative resections

Table 2. TIMING, TYPE, AND RESPONSE TO CHEMOTHERAPY (N = 37)

	Disease at Diagnosis		All Patients
	Localized/ Locoregional	Metastatic	
Type of chemotherapy			
VAC	14	3	17 (46%)
Other doxorubicin-based regimen	3	1	4 (11%)
MAID	7	6	13 (35%)
Other ifosfamide-based regimen	0	3	3 (8%)
Response to chemotherapy			
Complete	11	4	15 (41%)
Partial	7	5	12 (32%)
None	2	1	3 (8%)
Progression	1	2	3 (8%)
Unable to assess	3	1	4 (11%)

VAC, vincristine, Adriamycin, cyclophosphamide; MAID, mesna, Adriamycin, ifosfamide, dacarbazine.

consisting of either enucleation ($n = 2$) or subtotal excision ($n = 5$). Twenty-one patients underwent attempted curative resections including wide excision ($n = 17$), compartmental excision ($n = 2$), or amputation ($n = 2$). Among the 26 patients with localized or locoregional disease, 6 underwent complete resections, 7 underwent compromised resections, and 13 underwent biopsy alone or incomplete resections. Radiation therapy was administered to 24 patients (21 with localized disease, 3 with metastatic disease) to a median dose of 55 Gy (range 30–66). Most patients ($n = 16$) were treated after surgery; of these, two received additional brachytherapy at doses of 30 and 35 Gy.

The location of the primary tumor was correlated with the type of resection performed: 83% of patients with extremity tumors, 71% of patients with truncal tumors, and 57% of patients with genitourinary tract tumors underwent attempted curative resections, compared with only 15% of patients with head and neck tumors ($P = .008$). In addition, there was an association between the location of the tumor and the use of radiotherapy: 92% of patients with head and neck tumors received radiation, compared with 57%, 50%, and 29% of patients with truncal, extremity, and genitourinary tract tumors, respectively ($P = .02$). Fifty percent of patients who underwent complete resection received radiotherapy, versus 86% and 92% of patients who underwent partial or incomplete resection, respectively ($P = .1$).

Chemotherapy was used in 37 patients (95%; Table 2). Twenty-two patients received preoperative chemotherapy, and 15 patients were treated after surgery. Twenty-one patients were treated with doxorubicin-based regimens, and 16 patients were treated using ifosfamide-containing regi-

mens. No patients were treated with ifosfamide-containing regimens before 1985.

Response to Chemotherapy

Thirty-seven patients received systemic chemotherapy; of these, response to chemotherapy could be evaluated in 33 (89%; see Table 2). The overall response rate (i.e., complete or partial response) was 82%, with a complete response rate of 45%. Female patients had a higher complete response rate than male patients, although the difference was not statistically significant (64% vs. 31%, $P = .09$). There was a nonsignificant trend between tumor size and response to chemotherapy. Patients with tumors less than 5 cm, 5 to 10 cm, and more than 10 cm had complete response rates of 58%, 47%, and 17%, respectively ($P = .3$). There was no association between response to therapy and age, location, nodal involvement, stage at presentation, or histologic subtype. In addition, there was no association between response to therapy and timing or type of chemotherapy regimen.

Patterns of Failure

Thirty-five patients could be evaluated for local recurrence (four patients had bulky, residual disease after failed excision or chemotherapy). There were five local recurrences (14%), and all of them were isolated, with no patient having more than one local recurrence. One patient with a 7-cm tumor of the paranasal sinus was treated with irradiation (50.4 Gy) and systemic chemotherapy. After an initial complete response, disease recurred locally at 8 months (the end of the follow-up period). Three patients with large truncal/retroperitoneal tumors underwent attempted wide excisions with microscopically positive margins, and two received adjuvant radiotherapy (40 and 58 Gy). All three patients had poor responses to chemotherapy. Local recurrences were noted at 9, 15, and 17 months, and all three were dead within 3, 44, and 9 months, respectively. The final patient with a prostatic rhabdomyosarcoma underwent preoperative chemotherapy followed by enucleation of the tumor with microscopically positive margins. He did not receive radiotherapy, had local recurrence at 4 months, and died of distant disease at 11 months.

Thirty-one patients were evaluated for regional recurrence (the remainder had evidence of untreated nodal disease after local or systemic therapy). There were two regional recurrences (6%), and both patients had evidence of synchronous distant relapse. One patient with a uterine rhabdomyosarcoma underwent a radical hysterectomy/bilateral salpingoophorectomy with adjuvant chemotherapy, but disease recurred in the pelvis at 8 months. The second patient underwent a below-the-knee amputation for a foot tumor and received adjuvant chemotherapy, but disease recurred in the groin at 16 months. Neither patient received adjuvant radiotherapy, and both were dead within 18 and 10 months of their recurrence, respectively. Overall, the actu-

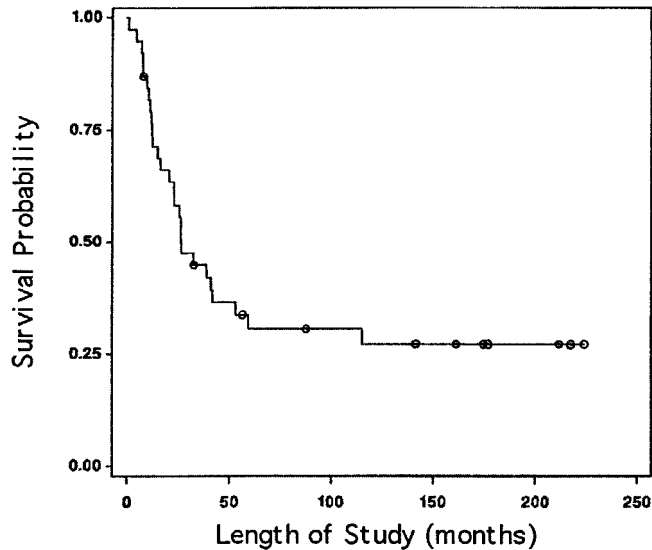


Figure 1. Overall survival rate for all patients ($n = 39$). Five- and 10-year survival rates were $31\% \pm 8\%$ and $27\% \pm 7\%$, respectively.

arial 5-year local and locoregional control rates were $83\% \pm 7\%$ and $76\% \pm 9\%$, respectively. Because of the small number of recurrences, statistical analyses looking at predictors of local and locoregional recurrence were not performed.

Thirty patients were evaluated for evidence of distant relapse (the other nine patients had evidence of residual metastatic disease after systemic chemotherapy). Fifteen patients (48%) suffered distant relapse after a median interval of 12 months (range 5–108). Two patients had synchronous regional relapse, and 13 patients had distant metastases as the first site of failure. Sites of distant metastases were not recorded. All patients with distant recurrence were dead at a median time of 10 months (range 1–36) after relapse.

Survival Analysis

The median follow-up was 26 months (range 1–224) for all patients and 152 months (range 8–224) for survivors. The overall 5- and 10-year survival rates in this series were $31\% \pm 8\%$ and $27\% \pm 7\%$, respectively (Fig. 1). The effects of the various demographic, histopathologic, and clinical variables on survival are summarized in Table 3. Patients with pleomorphic/NOS rhabdomyosarcomas were significantly older (46 years) than patients with embryonal (26 years) or alveolar (23 years) tumors ($P = .0008$). Age, however, was not associated with longer survival, irrespective of whether it was treated as a continuous or dichotomous variable. The 5-year survival rate for patients 26 years old or younger was 32%, compared with 29% for patients older than 26 years old ($P = .7$). Female patients showed a higher 5-year survival rate than male patients, but the difference was not statistically significant on univariate analysis (45% vs. 21%, $P = .1$). Histologic subtype appeared to

Table 3. OVERALL SURVIVAL ACCORDING TO PATIENT, TUMOR, AND CLINICAL CHARACTERISTICS (N = 39)

Prognostic Factor	5-Year Survival Rate (%)	Log-Rank <i>P</i> Value
Age		
≤ 26 yr	32 ± 11	.7
> 26 yr	29 ± 11	
Gender		
Female	45 ± 13	.1
Male	21 ± 9	
Location of primary		
Head and neck	42 ± 14	.3
Trunk	14 ± 13	
Genitourinary tract	0	
Extremity	39 ± 15	
Size of primary		
< 5 cm	60 ± 13	.0005
5–10 cm	14 ± 10	
> 10 cm	0	
Nodal involvement		
Negative	31 ± 10	.7
Positive	30 ± 11	
Stage at presentation		
3a-b	45 ± 13	$< .0001$
4a	44 ± 15	
4b	0	
Histologic subtype		
Embryonal	43 ± 19	.9
Alveolar	29 ± 10	
Pleomorphic/NOS	26 ± 15	
Response to chemotherapy (n = 33)		
Complete response	57 ± 13	.002
Poor response	7 ± 6	

NOS, not otherwise specified.

have some effect on survival, with 5-year survival rates of 43%, 29%, and 26% for embryonal, alveolar, and pleomorphic/NOS subtypes, respectively, but these differences were not statistically significant ($P = .9$).

The 5-year survival rates for patients with head and neck and extremity tumors were 42% and 39%, respectively, compared with 14% for patients with truncal tumors; there were no 5-year survivors among patients with genitourinary tract tumors ($P = .3$). Increasing tumor size was inversely related to prognosis (Fig. 2). The 5-year survival rates for patients with tumors less than 5 cm, 5 to 10 cm, and more than 10 cm were 60%, 14%, and 0%, respectively ($P = .0005$). Nodal involvement had no apparent effect on long-term survival. The 5-year survival rate for patients without evidence of nodal involvement was 31%, compared with 30% for patients with nodal disease ($P = .7$).

Figure 3 shows the effect of stage at presentation on survival. The 5-year survival rates for patients with localized (3a-b), locoregional (4a), and metastatic disease at

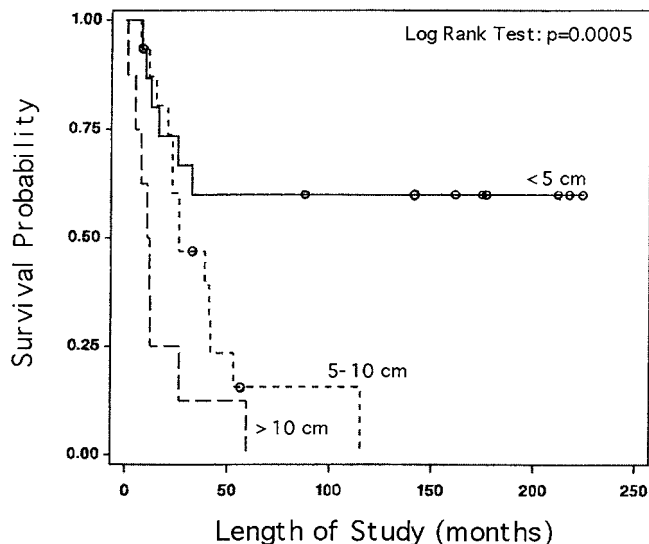


Figure 2. Overall survival rates for patients with primary tumors measuring less than 5 cm ($n = 15$), 5 to 10 cm ($n = 16$), and more than 10 cm ($n = 8$).

presentation (4b) were 44%, 45%, and 0%, respectively ($P < .0001$). Because the survivals for stage 3a and 4a patients were statistically equivalent, these patients were combined into a localized/locoregional group in the multivariate analysis. In this series, all the patients treated before 1985 had localized/locoregional disease. As a result, patients treated before 1985 had better survival; however, this difference was not significant once the analysis was stratified by stage at presentation.

Histologic subtype appeared to have an effect on survival, but the differences were not statistically significant ($P = .9$).

Complete response to chemotherapy was strongly associated with improved survival (Fig. 4). The 5-year survival

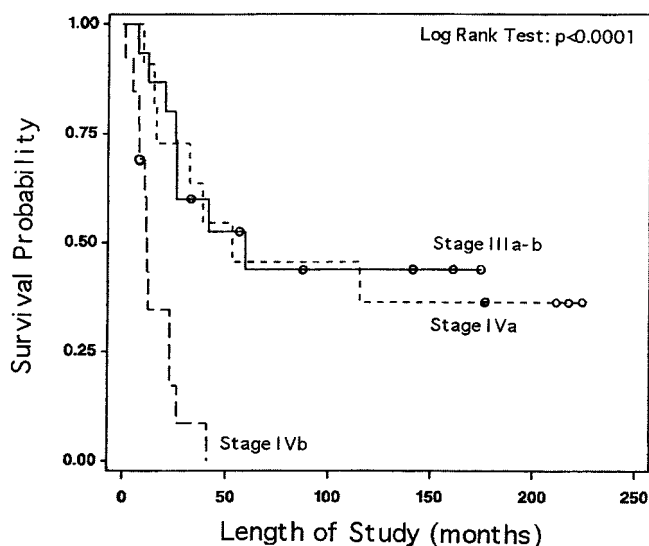


Figure 3. Overall survival rates for patients with stage 3a-b ($n = 15$), stage 4a ($n = 11$), and stage 4b ($n = 13$) disease at presentation.

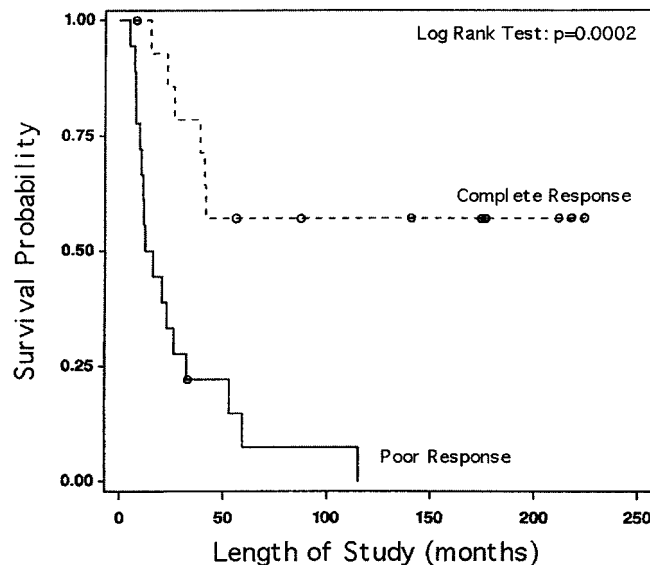


Figure 4. Overall survival rates for patients who had a complete response ($n = 15$) and poor response ($n = 18$) to systemic chemotherapy.

rate for complete responders was 57%, compared with 7% for patients who showed a partial response, showed no response, or had progression of their disease during chemotherapy ($P = .0002$). There was no association between the timing of chemotherapy or the type of regimen used and survival. The 5-year survival rates for patients who received preoperative versus postoperative chemotherapy were 23% and 38%, respectively ($P = .3$). Patients treated with doxorubicin-based regimens fared slightly better than patients treated with ifosfamide-containing regimens, but the difference was not statistically significant (35% vs. 25%, $P = .3$).

Tumor size, stage at presentation, and response to chemotherapy were entered into a multivariate model to identify independent predictors of long-term survival (Table 4). The following factors were significantly associated with death by Cox regression analysis: metastatic disease at presentation (hazard ratio = 9.0, $P < .0001$) and poor response to chemotherapy (hazard ratio = 6.0, $P = .0004$). Tumor size was not significant in the multivariate model, probably as a result of its association with both stage at presentation and response to chemotherapy. Thirteen percent of patients with tumors less than 5 cm had evidence of distant metastases at presentation, compared with 31% and

Table 4. INDEPENDENT PREDICTORS OF DEATH (N = 33)

Prognostic Factor	Hazard Ratio	P Value
Metastatic disease at presentation	9.0	<.0001
Poor response to chemotherapy	6.0	.0004

75% of patients with tumors measuring 5 to 10 cm and more than 10 cm, respectively ($P = .01$).

Finally, the effect of local therapy on long-term survival was analyzed. Patients who underwent successful complete resections fared slightly better than those who did not. Their 5-year survival rate was 63%, compared with 29% and 46% for patients who underwent compromised or incomplete resections, respectively ($P = .4$). Of the 26 patients who presented with localized or locoregional disease, 21 received adjuvant radiotherapy. Because of the small number of patients who did not receive radiotherapy, the impact of radiation therapy on overall survival could not be independently analyzed.

DISCUSSION

Rhabdomyosarcomas made up 3.6% of treated adult soft tissue sarcomas in a 1987 Pattern of Care Survey carried out by the American College of Surgeons.¹⁷ A review of 558 rhabdomyosarcomas evaluated at the Armed Forces Institute of Pathology during a 10-year period revealed that only 15% of cases were diagnosed in patients older than 15 years of age.¹⁸ Further, only 3% of cases in this series were diagnosed in patients older than 40 years.

The literature on adult rhabdomyosarcoma is limited. Three recent series of patients with rhabdomyosarcoma included a significant number of adults. Investigators at Stanford reviewed their experience treating adults with "childhood tumors," including 16 adults (21 years or older) with rhabdomyosarcoma.¹¹ Fourteen patients had advanced Intergroup Rhabdomyosarcoma Study (IRS) group disease, and all 16 patients were treated with multimodal therapy. After a maximum follow-up of 16 years, however, only five patients survived. A series published in 1983 from Memorial Sloan-Kettering Cancer Center consisted of 54 patients (age 20 years or older) with embryonal rhabdomyosarcoma.¹² Four, 16, 13, and 21 patients had head and neck, trunk, genitourinary tract, and extremity tumors, respectively. Six patients had distant metastatic disease. Forty patients received some form of local treatment (surgery, radiotherapy, or both), but only 10 patients received systemic chemotherapy. The overall 5-year survival rate in this series was 21%. A more recent series from Memorial Sloan-Kettering included 290 children, adolescents, and adults with rhabdomyosarcoma, but most of the patients were younger than 21 years.¹³ The authors noted a relative increase in the number of extremity tumors and pleomorphic subtype with increasing age. Forty-three percent of patients underwent complete resection, 67% received adjuvant radiotherapy, and 95% received systemic chemotherapy. The subsequent survival analysis was performed across all age groups (including children and adolescents), with an overall 5-year survival rate of 56% (95% confidence interval 50–62%). Adult patients were not analyzed as a separate group.

In the current series, we reviewed our experience with 39 adults with rhabdomyosarcoma to assess the response to

systemic chemotherapy and to identify predictors of response to chemotherapy and long-term survival. The overall 5-year survival rate in this series was $31\% \pm 8\%$. The independent predictors of long-term survival were localized/locoregional disease at presentation and complete response to chemotherapy. In addition, female gender and tumor size appeared to be associated with complete response to chemotherapy, although the associations were not statistically significant.

In infants and young children, rhabdomyosarcomas tend to involve the head and neck and genitourinary tract and are most often of the embryonal histologic subtype. In adolescents and adults, there is a greater predilection for truncal and extremity sites, as well as alveolar and pleomorphic subtypes. As a result, older age has often been perceived as an adverse predictor of survival, although its true effect is controversial in the pediatric literature.

Crist et al¹⁹ reviewed the effect of age in 1,688 children (younger than 21 years old) entered into IRS-I and IRS-II. Although there was a trend toward worse survival with increasing age (younger than 5 years vs. 6–10 years vs. 11–15 years vs. older than 15 years), the differences were not statistically significant except in two clinical groups in IRS-II, and the differences did not follow a linear trend.

In the latest series from Memorial Sloan-Kettering, the relative proportion of extremity and pleomorphic tumors increased with age, and survival decreased with increasing age in both univariate and multivariate analyses.¹³ In this series, increasing age was not associated with worse survival, regardless of whether it was treated as a continuous or dichotomous variable.

The effect of gender on survival is unclear in the pediatric literature. Two early series identified female gender as an adverse predictor of survival.^{20,21} An initial review of IRS-I identified male gender as an unfavorable prognostic factor,²² but a subsequent review of IRS-I and IRS-II failed to show an association between gender and outcome.¹⁹ Similarly, gender was not a prognostic factor in the latest series from Memorial Sloan-Kettering.¹³ In our series, female patients had a higher 5-year survival rate than male patients, but the difference was not statistically significant. In addition, there appeared to be an association between female gender and response to chemotherapy, although the association was of borderline statistical significance. This observation was somewhat unexpected and has not been noted previously in either the adult or pediatric literature. Although most female patients had alveolar tumors, there was no association between histologic subtype and response to chemotherapy, suggesting that the distribution of subtypes between genders does not explain the observed difference.

Children with head and neck tumors have traditionally fared better than children with extremity tumors, probably because of the higher percentage of alveolar tumors at these sites.¹ In infants and toddlers, genitourinary tract tumors usually present as embryonal rhabdomyosarcomas, often of the botryoides subtype. These tumors often respond to ra-

diation and chemotherapy and are associated with better outcomes, particularly among patients with advanced IRS disease.¹⁹ In this series, patients with head and neck and extremity tumors fared better than patients with truncal and genitourinary tract tumors, although the differences were not statistically significant. In addition, 57% of the genitourinary tract tumors displayed a nonembryonal subtype, and there were no 5-year survivors. Previous series of adults with prostatic and paratesticular rhabdomyosarcomas have reported similarly poor results, suggesting that the histology and natural history of genitourinary tract tumors may be significantly different in older patients.^{23,24} Most adult patients appear to present with widely disseminated disease and, despite good initial responses to chemotherapy, eventually die of their disease.

Tumor size was associated with poor survival in IRS-I and IRS-II.¹⁹ In both series from Memorial Sloan-Kettering, a tumor size larger than 5 cm was associated with worse survival on univariate and multivariate analyses.¹³ In this series, increasing tumor size was weakly associated with a poor response to chemotherapy and was significantly associated with worse survival on univariate analysis. There was a correlation between increasing tumor size and metastatic disease at presentation, and as a result, tumor size was not significant once the analyses were stratified by stage. The fact that tumor size failed to reach statistical significance in the multivariate analysis was likely due to this confounding effect, rather than sample size limitations.

Nodal involvement appears to be an adverse prognostic factor in both pediatric and adult rhabdomyosarcoma. A review of 1,415 patients without distant metastases in IRS-I and IRS-II revealed a 10% incidence of clinical nodal disease at diagnosis and a 14% incidence of pathologic lymphatic metastases at resection.²⁵ Nodal involvement was particularly common in patients with genitourinary tract tumors (prevalence 24–41%) and extremity tumors (12%), and the 3-year survival rate with locoregional disease was 45%, compared with 75% with localized disease. In La Quaglia et al's series,¹³ which included patients with distant metastatic disease, the rate of nodal disease was 28%, and 77% of patients had histologic verification by either biopsy or lymph node dissection. Nodal involvement was found to be a significant predictor of survival on both univariate and multivariate analysis. In our series, the rate of nodal involvement was 46%, and histologic verification was obtained in 13 of 18 (72%) patients. In our experience, nodal involvement did not appear to have a significant impact on survival, suggesting that isolated nodal disease does not preclude long-term survival in most patients treated with multimodal therapy.

The presence of metastatic disease at presentation was significantly associated with death on both univariate and multivariate analysis. Distant disease has been associated with poor outcome in several pediatric and adult rhabdomyosarcoma series.^{12,13,19} Patients with distant metastatic disease treated with escalating chemotherapeutic regimens

in IRS-I to IRS-III had shorter remissions and smaller gains in survival than their counterparts.^{8–10} This has prompted several groups to consider high-dose chemotherapy with hematopoietic rescue in children with recurrent and metastatic rhabdomyosarcoma.²⁶ Although preliminary reports are promising, it appears that patients with recurrent disease benefit more from these modalities than patients with primary metastatic disease.

In our series, patients with embryonal rhabdomyosarcoma did better than those with alveolar or pleomorphic/NOS histologic subtypes, but the difference was not statistically significant. Children with embryonal/botryoides histology have a better prognosis, particularly if they have localized, resectable disease.^{19,27} In La Quaglia et al's series,¹³ histologic subtype was associated with survival, but only if patients with pleomorphic tumors were included in the analysis. These results suggest that adults with embryonal and alveolar histologic subtypes have similar prognoses. Our inability to show a statistically significant relationship between subtype and survival may have resulted from the limited number of patients with pleomorphic/NOS tumors in our series.

There was a strong correlation between complete response to chemotherapy and long-term survival on both univariate and multivariate analysis. Complete response was in turn marginally associated with female gender and smaller tumor size. The impact of response to chemotherapy on survival was independent of the timing of the therapy or the type of regimen used. Our results suggest that systemic chemotherapy plays an important role in the management and salvage of adults with rhabdomyosarcoma. It remains to be seen whether the high-dose chemotherapy regimens used in children will hold similar promise in adults.

The 5-year survival rate in our series was 31%, well below the 56% to 65% and 56% rates reported in IRS-I to IRS-III and La Quaglia et al's series, respectively.^{8–10,13} Although these differences could be attributed to age, location of primary, and histologic subtype, the effect of metastatic disease must be considered. A third of our patients had evidence of distant metastases at presentation, compared with 17% to 19% and 23% of the patients in IRS-I to IRS-II and La Quaglia et al's series, respectively. Our survival figure compares favorably with the 21% rate reported by Lloyd et al¹² in 1983, despite a lower rate of metastatic disease in that series. Although the role of patient selection, improved surgical technique, and secular trends cannot be excluded, our 45% 5-year survival rate for stage 3a-4a disease and the observed association between the response to chemotherapy and long-term survival support the continued use of multimodal therapy in the management of rhabdomyosarcoma in adults. In the future, escalating chemotherapeutic regimens and novel systemic agents should perhaps be targeted to patients with localized/locoregional disease and partial responders to conventional chemotherapy to optimize their therapeutic impact and maximize overall survival.

References

1. Hays D. Rhabdomyosarcoma. In Welch K, ed. *Pediatric surgery*. Chicago: Year Book Medical Publishers, Inc; 1986:276–283.
2. Newton W, Gehan E, Webber B, et al. Classification of rhabdomyosarcomas and related sarcomas: pathologic aspects and proposal for a new classification: an Intergroup Rhabdomyosarcoma Study. *Cancer* 1995; 76:1073–1084.
3. Rosenberg A. Bones, joints, and soft tissue tumors. In Cotran R, ed. *Robbins' pathologic basis of disease*, 6th ed. Philadelphia: WB Saunders; 1999:1215–1268.
4. Brennan M, Casper E, Harrison L. Soft tissue sarcoma. In DeVita V, ed. *Cancer: principles and practice of oncology*, 5th ed. Philadelphia: Lippincott-Raven; 1997:1738–1788.
5. Ariel I, Briceno M. Rhabdomyosarcoma of the extremities and trunk: analysis of 150 patients treated with surgical resection. *J Surg Oncol* 1975; 7:269–287.
6. Stobbe G, Dargeon H. Embryonal rhabdomyosarcoma of the head and neck in children and adolescents. *Cancer* 1950; 3:826–836.
7. Stout A. Rhabdomyosarcoma of the skeletal muscles. *Ann Surg* 1946; 123:447–472.
8. Maurer H, Beltangady M, Gehan E, et al. The Intergroup Rhabdomyosarcoma Study I: a final report. *Cancer* 1988; 61:209–220.
9. Maurer H, Gehan E, Beltangady M, et al. The Intergroup Rhabdomyosarcoma Study II. *Cancer* 1993; 71:1904–1922.
10. Crist W, Gehan E, Ragab A, et al. The Third Intergroup Rhabdomyosarcoma Study. *J Clin Oncol* 1995; 13:610–630.
11. Prestidge B, Donaldson S. Treatment results among adults with childhood tumors: a 2-year experience. *Int J Radiat Oncol Biol Phys* 1989; 17:507–514.
12. Lloyd R, Hajdu S, Knapper W. Embryonal rhabdomyosarcoma in adults. *Cancer* 1983; 51:557–565.
13. La Quaglia M, Heller G, Ghavini F, et al. The effect of age at diagnosis on outcome in rhabdomyosarcoma. *Cancer* 1994; 73:109–117.
14. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457–481.
15. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J Roy Stat Soc A* 1972; 135:185–206.
16. Cox D. Regression models and life tables. *J Roy Stat Soc B* 1972; 34:187–220.
17. Lawrence W, Donegan W, Natarajan A, et al. Adult soft tissue sarcomas: a pattern of care survey in the American College of Surgeons. *Ann Surg* 1987; 205:349–359.
18. Enzinger F, Weiss S. *Soft tissue tumors*, 2d ed. St. Louis: CV Mosby; 1988:448–488.
19. Crist W, Garnsey L, Beltangady M, et al. Prognosis in children with rhabdomyosarcoma: a report of the Intergroup Rhabdomyosarcoma Studies I and II. *J Clin Oncol* 1990; 8:443–452.
20. Neifeld J, Maurer H, Godwin D, et al. Prognostic variables in pediatric rhabdomyosarcoma before and after multi-modal therapy. *J Pediatr Surg* 1979; 14:699–703.
21. Gehan E, Glover F, Maurer H, et al. Prognostic factors in children with rhabdomyosarcoma. *Natl Cancer Inst Monogr* 1981; 56:83–92.
22. Maurer H, Crist W, Donaldson M, et al. The Intergroup Rhabdomyosarcoma Study. *Cancer Bull* 1982; 34:108–110.
23. Russo P. Urologic sarcoma in adults: Memorial Sloan-Kettering Cancer Center experience based on a prospective database between 1982 and 1989. *Urol Clin North Am* 1991; 18:581–588.
24. Waring P, Newland R. Prostatic embryonal rhabdomyosarcoma in adults: a clinicopathologic review. *Cancer* 1992; 69:755–762.
25. Lawrence W, Hays D, Heyn R, et al. Lymphatic metastases with childhood rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study. *Cancer* 1987; 60:910–915.
26. Koscielnak E, Klingebiel T, Peters C, et al. Do patients with metastatic and recurrent rhabdomyosarcoma benefit from high-dose therapy with hematopoietic rescue? A report of the German/Austrian Pediatric Bone Marrow Transplantation Group. *Bone Marrow Transplant* 1997; 19:227–231.
27. Gaiger A, Soule E, Newton W. Pathology of rhabdomyosarcoma: experience of the Intergroup Rhabdomyosarcoma Study. *Natl Cancer Inst Monogr* 1981; 56:19–27.